The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte UWE BORNSCHEUER,
HARTMUT HERMANN MEYER
and JOSEF ALTENBUCHNER

Appeal No. 2005-1745
Application No. 09/161,680

ON BRIEF

ELLIS, SCHEINER and GREEN, Administrative Patent Judges.

ELLIS, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal pursuant to 35 U.S.C. § 134 of the examiner's final rejection of claims 12-27, all the claims pending in the application. Claims 1-11 have been cancelled.

Claims 12, 20 and 24 are representative of the subject matter on appeal and read as follows:

12. A method for generating a new catalytic activity in an enzyme, comprising the steps of:

a) introducing a DNA sequence coding for the enzyme into the Escherichia coli strain XL1-Red or into a functional derivative thereof which is also an E. coli strain carrying the genetic markers relA1, mutS, mutT and mutD5 and having an increased mutation rate,

b) incubating the transformed Escherichia coli strain XL1-Red or its functional derivative to generate mutations in the DNA sequence,

c) transferring the mutated DNA sequence from the transformed Escherichia coli strain XL1-Red or its functional derivative to a microorganism which has no enzyme activity which would impede selection,

d) incubating this microorganism to detect the new catalytic activity in at least one selection medium which comprises at least one enzyme substrate to recognize the newly generated catalytic activity in the enzyme, with or without other indicator substances, and

e) selecting the microorganisms which show the newly generated catalytic activity, said microorganisms in steps c), d), and e) being a member selected from the group consisting of bacteria, fungi and yeasts, wherein the enzyme is selected from the group consisting of lipases, amidases, nitrilases, ether hydrolases, peroxidases, glycosidases and phytases.

20. The method of claim 13, wherein the lipase is selected from the group of lipases consisting of Pseudomonas cepacia lipases PS, Pseudomonas cepacia lipase AH, acylase, Rhizopus delamar lipase, Rhizopus javanicus lipase, Candida rugosa lipase, Mucor javanicus lipase, Penicillium roquefortii lipase, Penicillium cyclopium lipase, Chromobacterium viscosum lipase, Rhizomucor miehei lipase, Humicola lanuginosa lipase, Candida antarctica lipase B and Candida antarctica lipase A.

24. A method for generating a new catalytic activity in an enzyme, wherein the new catalytic activity is within the same International Union of Biochemistry class as the enzyme's original catalytic activity, comprising the steps of:

a) introducing a DNA sequence coding for the enzyme into the Escherichia coli strain XL1-Red, or into a functional derivative thereof which is also an E. coli strain carrying the genetic markers relA1, mutS, mutT, and mutD5, and having an increased mutation rate,

b) incubating the transformed Escherichia coli strain XL1-Red or its functional derivative to generate mutations in the DNA sequence,

c) transferring the mutated DNA sequence from the transformed Escherichia coli strain XL1-Red or its functional derivative to a microorganism which has no enzyme activity which would impede selection,

d) incubating this microorganism to detect the new catalytic activity in at least one selection medium which comprises at least one enzyme substrate to recognize the newly generated catalytic activity, with or without other indicator substances, and

e) selecting the microorganisms which show the newly generated catalytic activity, said microorganisms in steps c), d) and e) being a member selected from the group consisting of bacteria, fungi and yeasts, wherein the enzyme is selected from the group consisting of lipases, amidases, nitrilases, ether hydrolases, peroxidases, glycosidases, phytases, and esterases selected from the group consisting of Pseudomonas fluorescens esterase, pig liver esterase and Thermoanaerobium brockii esterase.

The examiner does not rely on any references in rejecting the claims under the first and second paragraphs of 35 U.S.C. § 112.

The claims stand rejected as follows:

I. Claims 20 and 26 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

II. Claims 12-27 stand rejected under 35 U.S.C. § 112, first paragraph, as "failing to comply with the written description requirement." Answer, p. 3.

III. Claims 12-27 stand rejected under 35 U.S.C. § 112, first paragraph, for failing to provide an enabling disclosure of "methods using all enzymes, all substrates, and all possible mutator strains." Answer, p. 4.

IV. Claims 24-27 stand rejected under 35 U.S.C. § 112, first paragraph, as "failing to comply with the written description requirement." Answer, p. 4.

We affirm Rejection IV, reverse Rejections I and II, and need not reach the merits of Rejection III. In addition, we enter a new ground of rejection pursuant to 37 C.F.R. § 41.50(b) for all the claims.

Background

Enzymes are highly-specific protein catalysts. Two properties of enzymes are their catalytic power and their specificity. The present invention is said to be directed to methods of making enzymes which have a new catalytic activity using recombinant DNA technology. Specifically, the invention involves the use of a strain of Escherichia coli (E. coli) known as XL1-Red which is able to generate mutants at a greater rate than

the wild-type parent. The E. coli strain is said to generate "single-point mutations randomly within a cloned gene of interest . . . with just overnight growth." Greener, p. 376, col. 1.[1] Thus, by transforming this microorganism with vectors comprising a gene which codes for specific enzymes and growing them overnight, the appellants are said to generate enzymes having a new catalytic activity.

Discussion

Rejection I

The examiner contends that claims 20 and 26 are indefinite in the recitation of the phrases "'Pseudomonas cepacia lipase AH,' 'acylase' and 'Candida antarctica lipase A.'" Answer, p. 3. The examiner argues that (i) she has not found P. cepacia lipase AH from the same source as she found P. cepacia lipase PS; (ii) C. antarctica lipase A is not known in the art; and (iii) "the term 'acylase' is unclear as to its exact nature since several enzymes . . . have this synonym for their name." Office Action, mailed March 3, 2004, p. 4, para. 3. The examiner relies on an unidentified, and unattached, "attachment" for support.

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[1] Greener et al. (Greener), from Methods in Molecular Biology, "An Efficient Random Mutagenesis Technique Using an E. coli Mutator Strain," vol. 57, M. K. Trower, ed., Humana Press, Totowa, NJ, pp. 375-385 (1996), of record. See, PTO form 1449 filed by the appellants on November 30, 1999.

We point out that the analysis of whether the claims "set out and circumscribe a particular area with a reasonable degree of precision and particularity" involves reading the claims "in light of the teachings of prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art." In re Moore, 439 F.2d 1232, 1235, 169 USPQ 236, 238 (CCPA 1971).

The test of indefiniteness is not what the examiner has been able to locate in searching the prior art, but what one having ordinary skill in the art would have understood from reading the claims in light of the specification disclosure, in conjunction with what is known in the art. The words in the claims "are examined through the viewing glass of a person skilled in the art." Phillips v. AWH Corp., 415 F.3d 1303, 1326, 75 USPQ2d 1321, 1326 (Fed. Cir. 2005), quoting Home Diagnostics, Inc. v. LifeScan, Inc., 381 F.3d 1352, 1358, 72 USPQ2d 1276, 1279 (Fed. Cir. 2004). See also, Verve, LLC v. Crane Cams Inc., 311 F.3d 1116, 1119, 65 USPQ2d 1051, 1054 (Fed. Cir. 2002)(patent documents are meant to be "a concise statement for persons in the field") and In re Nelson, 280 F.2d 172, 181, 126 USPQ 242, 251 (CCPA 1960)("The descriptions in patents are not addressed to the public generally, to lawyers or to judges, but, as section 112 says, to those skilled in the art to which the invention pertains or with which it is most nearly connected"). Our reviewing court explained in Multiform Desiccants, Inc. v. Medzam Ltd., 133 F.3d 1473, 1477, 45 USPQ2d 1429, 1432 (Fed. Cir. 1998):

> It is the person of ordinary skill in the field of the invention through whose eyes the claims are construed. Such person is deemed to read the words used in the

> patent documents with an understanding of their meaning in the field, and to have knowledge of any special meaning and usage in the field. The inventor's words that are used to describe the invention – the inventor's lexicography – must be understood and interpreted by the court as they would be understood and interpreted by a person in that field of technology.

Although the examiner states that she has relied on some form of evidence to support her position, said evidence was neither attached to the electronic copy of the office action, nor does it appear to be elsewhere in the electronic file. We do not find this omission to be fatal given the strong opposing evidence provided by the appellants. That is, the appellants provide ample evidence which demonstrates that two of the enzymes which the examiner questions were known in the art and were commercially available at the time of the effective filing date of the appellants' application. Specifically, with respect to the P. cepacia lipase AH and the C. antarctica lipase A, the appellants provide information posted on the Amano Enzyme, Inc., the Sanger Institute, the German Collection of Microorganisms and Cell Cultures (DSMZ), and the Novozymes A/S websites which show that these enzymes are commercially-available products. Brief, pp. 5-7; attachments to the amendment received by the USPTO (U.S. Patent and Trademark Office) on September 16, 2003. Thus, we find that the phrases P. cepacia lipase AH and the C. antarctica lipase A do not require elaborate interpretation. Since the evidence of record demonstrates that a person skilled in the art at the time of the invention would have understood the meaning of Pseudomonas cepacia lipase AH and Candida antarctica lipase A, we find that the claims "set out and circumscribe" the invention to one of ordinary skill in the art "with a reasonable degree

of precision and particularity." In re Moore, 439 F.2d at 1235, 169 USPQ at 238; see also, Phillips v. AWH Corp., 415 F.3d at 1326, 75 USPQ2d at 1327("in some cases . . . claim construction . . . involves little more than the application of the widely accepted meaning of commonly understood words").

The term "acylase," however, stands on a different footing. Here, we note that the appellant does not contest the examiner's argument in this regard. Usually, findings of the examiner which are not challenged are accepted as fact. See, In re Kunzmann, 326 F.2d 424, 425 n. 3, 140 USPQ 235, 236 n. 3 (CCPA 1964). However, in this case, we find that the problem is not one of indefiniteness, but rather one of lack written descriptive support in the specification, as originally filed. Accordingly, we have set forth a new ground of rejection pursuant to 37 C.F.R. § 41.50(b), below.

In view of the foregoing, Rejection I is reversed.

Rejection II

The examiner argues that the specification disclosure of a single mutated enzyme does not provide written descriptive support for the claimed genus of "generating new enzymes using any enzyme and any substrate to produce a new enzyme (mutated with respect to the original enzyme) with altered substrate specificity relative to the original . . . because no correlation between the structures and functions of the reagents used in the methods is described." Answer, p. 4.

To satisfy the written description requirement, the inventor "must . . . convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). However, it is not necessary for the specification to describe the claimed invention ipsissimis verbis; all that is required is that it reasonably convey to those skilled in the art that, as of the filing date sought, the inventor was in possession of the claimed invention. Union Oil of California v. Atlantic Richfield Co., 208 F.3d 989, 997, 54 USPQ2d 1227, 1232 (Fed. Cir. 2000); Vas-Cath Inc. v. Mahurkar, 935 F.2d at 1563-64, 19 USPQ2d at 1119; In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989); In re Edwards, 568 F.2d 1349, 1351-52, 196 USPQ 465, 467 (CCPA 1978).

We find the examiner's arguments to be misdirected. Contrary to said arguments, we find that the problem with respect to the written description requirement goes to the issue of whether the specification, as originally filed, provides an adequate written description of the invention as now claimed. That is -- has new matter been added to the claims?

It is well established that when new matter is added to the claims, the proper course of action is to reject said claims for failing to satisfy the written description requirement of §112, first paragraph. In re Rasmussen, 650 F.2d 1212, 1214, 211 USPQ 323, 326 (CCPA 1981)("The proper basis for rejection of a claim amended to recite elements thought to be without support in the original disclosure, therefore, is

§ 112, first paragraph ..."). The purpose of the written description requirement is to "ensure that the scope of the right to exclude, as set forth in the claims does not overreach the scope of the inventor's contribution to the field as far as described in the patent specification." Reiffin v. Microsoft Corp., 214 F.3d 1342, 1345, 54 USPQ2d 1915, 1917 (Fed. Cir. 2000). As discussed above, to satisfy the written description requirement, the inventor "must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention" [first emphasis added]. Vas-Cath Inc. v. Mahurkar, 935 F.2d at 1563-64, 19 USPQ2d at 1117. "One shows that one is 'in possession' of the invention by describing the invention, with all its claimed limitations." [emphases in original]). Lockwood v. American Airlines, 107 F.3d 1563, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

Here, we point out that the claims, as originally filed, were directed to a "method for altering the substrate specificity of enzymes." In addition, the specification, as originally filed, disclosed, inter alia:

> Alteration of the substrate specificity in the novel method means that the enzymes having been subjected to the method are able to convert substrates which they were previously unable to convert, because the affinity of the enzyme for the substrate was too low (= high K_M) and/or the catalytic activity (= k_{cat}) of the enzymes was too low. In these cases, the ratio of k_{cat}/ K_M is zero or almost zero, i[.]e.[,] catalysis does not occur. The alteration in the substrate specificity reduces the K_M or increases the k_{cat}, or both, i[.]e.[,] the ratio of k_{cat}/ K_M becomes greater than zero. A catalytic reaction occurs. The enzyme converts the new substrate after the mutagenesis. [Specification, p. 3, line 42- p. 4, line 5].

The examiner rejected original, or now cancelled, claims 1, 2, 4-7 and 11 under 35 U.S.C. § 112, second paragraph, as being indefinite, inter alia, in the recitation of "substrate specificity." According to the examiner, "the art defines substrate specificity by k_{cat}/ K_M; the 'greater than zero' phrase in the specification is unclear. Claim 1, the first 4 lines[2] describing this method are unclear in view of this definition." See, the final office action, mailed January 4, 2002, p. 6.

In response, the appellants filed an amendment to the claims on June 10, 2002, canceling all pending claims and adding new claims 12-23. The newly added claims 12-23 were directed to a "method for altering the substrate specificity of an enzyme." The examiner continued to reject the claims as being indefinite in the recitation of "substrate specificity." Office Action, mailed December 10, 2002, p. 5.

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[2] The first 4 lines of original claim 1 read as follows:

> 1. A method for altering the substrate specificity of enzymes, which comprises carrying out the following steps:
>
> a) introducing a DNA which comprises a copy of the gene coding for the enzyme into the Escherichia coli strain

The examiner's next response (Office action, mailed December 10, 2002, p. 5), stated:

> . . . As noted for the previously pending claims that had been rejected on this basis, the specification loosely defines "substrate specificity" in the following sentence from page 4, lines 1-3: "The alteration in the substrate specificity reduces the K_M or increases the k_{cat}, or both, i.e. the ratio of k_{cat}/ K_M becomes greater than zero." As the Examiner has previously noted, the art defines substrate specificity by k_{cat}/ K_M; the "greater than zero" phrase in the specification is unclear. Moreover, on page 6, the specification seems to equate "altered substrate specificity" simply with the "(=mutations in the enzyme used)".[3] This is wholly unclear. Nowhere in the specification can a clear definition of the term "substrate specificity" be found. Thus, its metes and bounds are unclear.

The appellants then filed an amendment changing claims 12-23 to a "method for generating new catalytic activity in an enzyme." See, the amendment received by the USPTO on April 15, 2003. The amended, as well as the newly added, claims were directed to "[a] method for generating a new catalytic activity in an enzyme." In addition, the specification was amended, inter alia,[4] to read (at p. 3, line 42- p. 4, line 5), as follows:

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[3] As we understand it, the examiner is referring to the section of page 6, lines 4-9, in the originally-filed specification which read as follows:

> For detection of the altered substrate specificity (= mutations in the enzyme used) it is possible and advantageous, in the case where vectors have been used, for the DNA initially to be isolated from the E. coli strain XL1 Red or its functional derivative and be inserted into a microorganism which has no corresponding enzyme activity (step c, Figure 1).

[4] Page 6, as well as other sections of the specification were also amended by deleting reference to an altered substrate specificity and inserting thereto "newly generated catalytic activity."

> Generation of new catalytic activities ~~Alteration of the substrate specificity~~ in the novel method means that the enzymes having been subjected to the method are able to convert substrates which they were previously unable to convert, because the affinity of the enzyme for the substrate was too low (i.e., = high K_M) and/or the rate of conversion ~~catalytic activity~~ (= k_{cat}) of the enzymes was too low. In these cases, the ratio of k_{cat}/ K_M is zero or almost zero, i.e., catalysis does not occur. The generation of a new catalytic activity ~~alteration in the substrate specificity~~ reduces the K_M or increases the k_{cat}, or both~~, i.e., the ratio of k_{cat}/ K_M becomes greater than zero~~. A catalytic reaction occurs. The enzyme converts the new substrate after the mutagenesis [Amendment, received April 15, 2003, p. 14].

The appellants stated that because (i) the specification describes the invention "in terms of substrate/enzyme binding (K_M) and rate of conversion (k_{cat}); and (ii) "catalytic activity is the presently accepted term of art denoting the combined effect of these factors,"[5] the amendments to the specification did not introduce any new matter. The amendment received April 15, 2003, p. 3.

In response, the examiner dropped the aforementioned rejection under § 112, second paragraph, and finally rejected the claims in the office action mailed July 1, 2003.

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[5] The appellants argue in the amendment received April 15, 2003, that:

> Enzymic activity, according to the Oxford Dictionary of Biochemistry and Molecular Biology, is "the rate of reaction of substrate that may be attributed to catalysis by an enzyme (p. 210, see attached excerpt). It is "now obsolete" and has been superceded by the term "catalytic activity" (id.). Catalytic activity of an enzyme, in turn, is defined as "the property measured by the increase in the rate of conversion of a specified chemical reaction that the enzyme produces in a specified assay system. . . . [I]t is . . . conceptually different from rate of conversion although measured by and equidimensional with it" (id., p. 97).

The appellants then filed an amendment on September 16, 2003,[6] amending claims 12-23; and adding claims 24-27. In addition, the appellants again amended several sections of the specification. With respect to the aforementioned (p. 3, line 42-p. 4, line 5), the specification was changed to read:

> Generation of new catalytic activities in the novel method means that the enzymes having been subjected to the method are able to convert substrates which they were previously unable to convert, because the affinity of the enzyme for the substrate was too low (i.e., high K_M) and/or the rate of conversion (k_{cat}) ~~too low (i.e., = high K_M) and/or the rate of conversion (= k_{cat})~~ of the enzymes was too low. In these cases, the ratio k_{cat}/ K_M is zero or almost zero, i.e., catalysis does not occur. The generation of a new catalytic activity reduces the K_M or increases the k_{cat}, or both. A catalytic reaction occurs. The enzyme converts the new substrate after the mutagenesis [Amendment, received September 16, 2003, p. 11].

Contrary to the appellants' arguments, we find that each of the aforementioned amendments introduced new matter to the specification. 35 U.S.C. § 132. In addition, because the appellants also amended the claims so that they are now directed to "[a] method of generating a new catalytic activity in an enzyme," we find that they contain subject matter which was not described in the specification, as originally filed. 35 U.S.C. § 112, first paragraph.

Accordingly, Rejection II is reversed and we have set forth new ground of rejection pursuant to 37 C.F.R. § 41.50(b) for claims 12-27. Attention is directed to our discussion, infra.

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[6] It appears that the amendment filed on September 16, 2003 was not entered until November 6, 2003.

Rejection III

Given our disposition of Rejection II, we need not reach the merits of Rejection III.

Rejection IV

The examiner contends that the specification, as originally filed, does not provide written descriptive support for the concept of using the claimed method "to generate a 'new catalytic activity . . . within the same International Union of Biochemistry class as the enzyme's original activity.'" Answer, p. 5. Thus, the examiner finds that the specification fails "to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the" invention described in claims 24-27. Id.

In response, the appellants argue that support for the claim language can be found in the specification on "page 4, line 10," and in the example which begins on page 11. Brief, p. 10. We find this argument unpersuasive.

As a preliminary matter, we point out that in our deliberation of this issue we considered "page 4, line 10," and the example which begins on page 11, of the specification, as originally filed, and not any of the appellants' aforementioned amendments thereto. See pages 13-14, above.

Here, we find that the appellants added the contested phrase to the claims in the amendment received by the USPTO on September 16, 2003 (entered November 6, 2003). As discussed above, when new subject matter is added to the claims, the proper course of action is to reject said claims under § 112, first paragraph. In re Rasmussen, 650 F.2d at 1214, 211 USPQ at 326. As further discussed above, to satisfy the written description requirement, the inventor "must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention" [emphasis added]. Vas-Cath Inc. v. Mahurkar, 935 F.2d at 1563-64, 19 USPQ2d at 1117.

We have carefully reviewed the sections of the specification relied upon by the appellants and find that page 4, lines 7-13, as originally filed, state, in relevant part, that

> It is possible in principle for the substrate specificity of all enzymes to be altered, and preferably the substrate specificity of hydrolases is altered in the novel method. Hydrolases form the 3rd class of enzyme (= 3 . .) in the IUB nomenclature system. Hydrolases are preferred in the novel method because, as a rule, a simple detection reaction for them exists and, in many cases they are used in industrial syntheses.

We further find that Example 2, on pages 11-12, describes the assay used to determine esterase activity. In this regard, the specification simply states that "[t]he esterase activity has been reported in units, where one unit (= U) is defined as the amount of enzyme which produces 1 µmol of acetic acid per minute under the assay conditions." Specification, p. 11, line 46- p. 12, line 2. Contrary to the appellants' argument, we do not find that either of the aforementioned sections of the specification, as originally filed, describe a method of generating an enzyme having new catalytic

activity which "is within the same International Union of Biochemistry class as the enzyme's original catalytic activity." Thus, we agree with the examiner that the addition of this phrase to claims 24-27 constitutes new matter.

Accordingly, Rejection IV is affirmed.

V. New Ground of Rejection

Pursuant to 37 C.F.R. § 41.50(b), we set forth the following new grounds of rejection.

A. Claims 20 and 26

Claims 20 and 26 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed.

We point out that claims 20 and 26 were added to the specification by amendment filed June 10, 2002, and September 16, 2003 (entered on November 6, 2003), respectively. The claims are directed to a group of enzymes which includes, inter alia, acylase. However, we do not find, and the appellants have not pointed out, any section(s) in the specification, as originally filed, which provide written descriptive support for this type of enzyme.

As discussed above, when new matter is added to the claims, the proper course of action is to reject said claims for failing to satisfy the written description requirement of § 112, first paragraph. In re Rasmussen, 650 F.2d at 1214, 211 USPQ at 326. As further discussed above, to satisfy the written description requirement, the inventor "must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention" [first emphasis added] (Vas-Cath Inc. v. Mahurkar, 935 F.2d at 1563-64, 19 USPQ2d at 1117); and "One shows that one is 'in possession' of the invention by describing the invention, with all its claimed limitations . . ." [emphases in original]) (Lockwood v. American Airlines, 107 F.3d at 1572, 41 USPQ2d at 1966). As still further discussed above, it is not necessary for the specification to describe the claimed invention ipsissimis verbis; all that is required is that it reasonably convey to those skilled in the art that, as of the filing date sought, the inventor was in possession of the claimed invention. Union Oil of California v. Atlantic Richfield Co., 208 F.3d at 997, 54 USPQ2d at 1232; Vas-Cath Inc. v. Mahurkar, 935 F.2d at 1563-64, 19 USPQ2d at 1119; In re Gosteli, 872 F.2d at 1012, 10 USPQ2d at 1618; In re Edwards, 568 F.2d at 1351-52,196 USPQ at 467.

Accordingly, since the specification, as originally filed, does not provide any description of using the claimed method to generate a new catalytic activity for an acylase, we find that claims 20 and 26 fail to comply with the written description requirement of 35 U.S.C. § 112.

B. Claims 12-26

Claims 12-26 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed.

As discussed above, the specification, as originally filed, does not provide an adequate written description of a method "for generating a new catalytic activity in an enzyme."

Enzymes are proteins that act as catalysts. "The chemicals that undergo a change in a reaction catalyzed by an enzyme are the substrates of that enzyme." Darnell, p. 55, col. 2, para. 3.[7] "Enzyme molecules have two important regions, or sites: one that recognizes and binds the substrate(s), and one that catalyzes the reaction once the substrate(s) have been bound. . . . In some enzymes the catalytic site is part of the substrate-binding site. These two regions are called, collectively, the active site." Id., p. 56, col. 1, para. 2. "The specificity of an enzyme is determined by the different rates at which it catalyzes closely similar chemical reactions or by its ability to distinguish between closely similar substrates." Id., para. 1. With either event, the first step in enzyme catalysis requires the binding of the enzyme to the substrate. In this regard, there are two mechanisms of interaction. One is known as the "lock and key"

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[7] Darnell et al. (Darnell), Molecular Cell Biology, 2nd Edition, Scientific American Books, distributed by W.H. Freeman and Company, NY, 1990. Relevant pages attached.

mechanism whereby the enzyme and substrate simply fit together forming "a complex stabilized by a variety of noncovalent bonds." Darnell, p. 60, para. 1. The other mechanism, known as "induced fit" occurs when

> the substrate induces a conformational change in the enzyme that causes the catalytic residues to become positioned correctly. Molecules that attach to the substrate-binding site, or recognition site, of the enzyme but that do not induce a conformational change are not substrates of that enzyme. Thus an enzyme differentiates between a substrate and a nonsubstrate in two ways: Does the potential substrate bind to the enzyme? If so, does it produce a conformational change? When both criteria are met, the enzyme-substrate complex is said to demonstrate an induced fit [second emphasis added] Darnell, p. 60, para. 2.

The same is true with the "lock and key" mechanism of interaction. There the enzyme must bind to the substrate albeit by noncovalent bonds. Thus, the statement in the specification, as originally filed, that "[a]lteration of substrate specificity in the novel method means that enzymes having been subjected to the method are able to convert substrates which they were previously unable to convert," could be interpreted to mean that the method results in the production of enzymes which "bind" or interact, either by "lock and key" or "induced fit," with a completely new substrate.

We recognize that the specification, as originally filed, further states that the enzymes were unable to convert the new substrates "because the affinity of the enzyme for the substrate was too low (= high K_M) and/or the catalytic activity (= k_{cat}) of the enzyme is too low." Specification, p. 3, lines 45-47. These properties of affinity and/or activity differ from the enzyme's structural interactions and thus are the source of the examiner's concerns. As set forth in the specification, K_M measures the affinity of the enzyme for the substrate. The K_M (the Michaelis-Menten constant) expresses "the

mathematical relationship between the initial rate of an enzyme-catalyzed reaction, the concentration of the substrate, and certain characteristics of the enzyme." Lehninger, p. 190.[8] That is,

> Because of the way that enzymes work, there is a limit to the amount of a substrate that a single enzyme can process at a given time. If the concentration of substrate is increased, the rate at which product is formed also increases up to a maximum value. . . . At that point the enzyme molecule is saturated with substrate [Alberts,[9] p. 131, para. 1].

The K_M "is equal to the substrate concentration at which the initial reaction velocity is half maximal." Lehninger, p. 193, para. 1. Thus, "[a] low K_M value means that the enzyme reaches its maximum catalytic rate at a low concentration of substrate and generally indicates that the enzyme binds its substrate very tightly." Alberts, p. 131, para. 2. Accordingly, the disclosure on page 3, lines 45-46, of the specification, as originally filed, that the K_M value of the enzyme to the substrate was high, means that the enzyme had very little affinity for the substrate. Nevertheless, to have a K_M value at all, there must be some binding of the enzyme and substrate, albeit with very low affinity (i.e., high K_M). Thus, the statement in the specification with respect to the enzyme having any K_M value appears to be inconsistent with the statement that the enzyme was previously unable to convert the substrate.

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[8] Lehninger, in Biochemistry, 2nd Edition, Worth Publishers, Inc., New York (1975). Relevant pages attached.

[9] Alberts et al. (Alberts), in Molecular Biology of the Cell, Garland Publishing, Inc., New York and London (1983). Relevant pages attached.

The catalytic activity (k_{cat}) is a quantitative measure, which according to the appellants, is the rate at which the substrate is converted into product by the enzyme. Amendment received April 15, 2003, p. 3. The rate at which the product is formed depends, inter alia, on the concentration of substrate and on the enzyme itself, and on the concentration of the enzyme. Alberts, p. 61. Thus, lack of catalytic activity is one reason why an enzyme may be unable to convert a substrate to a product. However, in order for the enzyme to be able to convert the substrate to a product, it must, as discussed above, first bind to the substrate.

The preceding may be "much ado about nothing." The problem here is that in trying to rectify this confusion, the appellants changed the specification, as originally filed, from "alteration of the substrate specificity" of an enzyme as meaning that an enzyme is unable to convert substrate(s) it previously could not convert because of said enzyme's affinity (K_M) and catalytic activity (k_{cat}), to "generating a new catalytic activity [k_{cat}]" for an enzyme so that it is able to convert substrates it could not previously convert because of enzyme affinity (K_M) and rate of conversion. Whether one statement is more accurate or clear is immaterial, the statements are not equivalent. Regardless of whatever are now the "in vogue" terms of art,[10] the amendments to the specification

[10] According to the appellants', the phrase "enzymic activity" is "'now'obsolete' and has been superseded by the term 'catalytic activity.'" Amendment, received April 15, 2003, p. 3. We point out, however, the original claims were directed to a method of altering the substrate specificity of an enzyme, and not to a method of altering the enzymic activity of an enzyme. Thus, the amendment to the claims to " a method for generating a new catalytic activity of an enzyme," constitutes the addition of new matter.

demonstrate that a method of altering the substrate specificity of an enzyme (as set forth in the original claims) and a method of generating a new catalytic activity of an enzyme (as set forth in the present claims) are not the same. In addition, the specification, as originally filed, disclosed the alteration of substrate specificity due, inter alia, to an enzyme previously being unable to convert a substrate because of a low catalytic activity. We point out that as a result of the amendments, the claims are now directed to generating a new catalytic activity which encompasses both an increase and a decrease in said activity; whereas, the claims, as originally filed, encompassed only an increase in substrate specificity since the enzyme was able to convert a substrate that it was previously unable to convert. Thus, since the specification, as originally filed, does not provide an adequate written description a method of "generating a new catalytic activity," we find that it [the specification] does not "convey with reasonable clarity to those skilled in the art that, as of the filing date sought" that they were in possession of the invention as now claimed. Lockwood v. American Airlines, 107 F.3d at 1572, 41 USPQ2d at 1966; Vas-Cath v. Mahurkar, 935 F.2d at 1563-64, 19 USPQ2d at 1117.

VI. Another issue

In the event of further prosecution, the examiner may wish to consider whether the claims are patentable under 35 U.S.C. § 103 in view of Greener alone or in combination with another reference. Greener discloses a method of generating a new catalytic activity with two enzymes, β-lactamase and alkaline phosphatase, by introducing a DNA sequence encoding said enzymes into the E. coli strain XL1-Red and incubating the transformed E. coli to generate mutations in the DNA sequence. Greener further discloses transferring the mutated DNA sequence into a strain which lacked the enzyme activity, incubating this strain in the presence of a selection medium, and selecting microorganisms "which have increased (or decreased) activity." Greener, p. 383, para. 8. Greener still further discloses the XL1-Red mutator strain can be used "for introducing random mutations in a cloned gene when a genetic selection or screen for variants is available." Id., p. 384, last para. Greener still further discloses that "[t]he advantage in using XL1-Red for random mutagenesis (over e.g., chemical mutagenesis or a PCR-based protocol) is that the mutation rate can be carefully controlled". Id. Thus, the examiner may wish to consider whether the present method would have been obvious in view of these teachings in combination with teachings of cloned enzyme genes.

Regarding the affirmed rejection(s), 37 CFR § 41.52(a)(1) provides "[a]ppellant may file a single request for rehearing within two months from the date of the original decision of the Board."

In addition to affirming the examiner's rejection(s) of one or more claims, this decision contains a new ground of rejection pursuant to 37 CFR § 41.50(b) (effective September 13, 2004, 69 Fed. Reg. 49960 (August 12, 2004), 1286 Off. Gaz. Pat. Office 21 (September 7, 2004)). 37 CFR § 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review."

37 CFR § 41.50(b) also provides that the appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

> (1) *Reopen prosecution.* Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the proceeding will be remanded to the examiner. . . .
>
> (2) *Request rehearing.* Request that the proceeding be reheard under § 41.52 by the Board upon the same record. . . .

Should the appellant elect to prosecute further before the examiner pursuant to 37 CFR § 41.50(b)(1), in order to preserve the right to seek review under 35 U.S.C. §§ 141 or 145 with respect to the affirmed rejection, the effective date of the affirmance is deferred until conclusion of the prosecution before the examiner unless, as a mere incident to the limited prosecution, the affirmed rejection is overcome.

If the appellant elects prosecution before the examiner and this does not result in allowance of the application, abandonment or a second appeal, this case should be returned to the Board of Patent Appeals and Interferences for final action on the affirmed rejection, including any timely request for rehearing thereof.

AFFIRMED IN PART; NEW GROUND OF REJECTION

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Toni R. Scheiner) BOARD OF PATENT
Administrative Patent Judge)
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